Effects of Statin Therapy in Patients with Stroke and Atheromatosis

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Recent studies have shown that as the average life expectancy increases, more people will suffer a stroke in their lives, diminishing their quality of life. Secondary stroke prevention involves reducing the cardiovascular risk factors and administering medication for preventive purposes, where statins play an important role. The purpose of this study is to highlight the correlations of statins dosage with cardiovascular risk factors (atheromatosis, uric acid value, obesity, etc), in stroke patients receiving hypolipidemic treatment with statins.

Keywords: statins, stroke, uric acid, liver enzymes

Stroke is the third cause of morbidity and mortality worldwide, both in Europe and the US, after ischemic heart disease and oncologic pathology [1-3]. Like many other pathologies, stroke results from the interaction between genetic predisposition and environmental factors. Genetic risk factors cannot be changed, while lifestyle consists of behavioural components that can be improved. Unchangeable risk factors for stroke are: age, familial antecedents, race, sex, previous vascular events. The modifying risk factors include: arterial hypertension, diabetes mellitus, atrial fibrillation, asymptomatic carotid atheromatosis, cardiac disease, hypercholesterolemia, obesity, smoking, sedentarism, poor socio-economic condition, drug use or alcohol abuse [4]. Secondary prevention already involves administration of preventive medication (anti-aggregation, hypolipidemic, antihypertensive), depending on aetiology and associated diseases [5-7]. Two very important risk factor in the etiology of stroke (both constituted and transient) are atherosclerosis and dyslipidemia [8-10]. Consequently, following the international guidelines in force recommend the use of statins in patients with a history of stroke as a prognostic element with a double action: to lower cholesterol and triglyceride levels and to stabilize carotid or cerebral atheroma plaques [7, 11, 12]. According to the 2016 ACC/AHA blood cholesterol management guidelines, the usage of statins in secondary prevention showed a reduction of 16% for stroke, of 27% for nonfatal myocardial infarction and 20% for mortality from cardiac events [13-15].

Excessive and/or long-term use of statins can cause cytotoxicity, hepatic injury or necrosis, kidney damage and myopathy [16,17]. Periodically monitoring of hepatic and kidney function, as well as muscular enzymes, are needed to prevent any undesirable effects [18,19]. Besides their effect on muscle liver and kidney, many studies found evidence connecting statins to new-onset of diabetes mellitus, cognitive impairment and haemorrhagic stroke [20,21]. However, the existing literature and guidelines suggest that the benefits of statin therapy outweigh any adverse effects or risks [22].

Experimental part

The purpose of this study is to highlight the correlations between the value of statins and other cardiovascular risk factors (diabetes, atheromatosis, uric acid value) in patients with stroke receiving hypolipidemic therapy with statins as secondary prevention. Also, we monitored the side effects of statins by analyzing the liver enzymes.

In our retrospective study, we included 58 patients with a history of ischemic stroke, hospitalized between 01.01-30.09.2018 in the Neurology Department inside the Clinical Rehabilitation Hospital in Iasi, Romania. All patients were assessed for anthropometric measurements (age, weight, height, BMI), biochemical analysis: hepatic enzymes, uric acid, glycemia, glycosylated hemoglobin and lipid profile. Doppler cervical ultrasound was also performed at the level of the bilateral common carotid artery for the identification of atheromatosis and its degree, with a Siemens Accuson X300 system using a 7.5 MHz linear probe through a standardized method [23]. Patients with arterial occlusion or embolic stroke were excluded. All subjects before being examined and included were informed of the research method and signed an informed consent. Statistical analysis was performed with SPSS v.18. In interpreting statistical results we considered $p=0.005$ as the reference value for significance, which corresponds to a confidence interval of 95%. Continuous type variables were presented as mean ± standard deviation.

In our study we had 23 females and 35 males, with mean age 65.9±13.11 years. Most patients had a history of elevated blood pressure (82.8% vs.17.2%) and also presented with atheroma plaques in the carotid artery at the Doppler examination (53.4% vs.46.5%). 36.2% of the

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	AST	ALT	Uric acid	Cholesterol	Triglycerides
Mean	25.5500	36.7741	4.5569	145.7848	116.7788
Std. Deviation	17.78476	36.76194	1.73366	40.45919	56.29924
Minimum	11.00	10.60	1.26	85.80	43.40
Maximum	106.60	191.60	8.16	256.00	302.00

Table 1
BIOLOGICAL ANALYSIS FOR THE STUDY GROUP

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Without	7	12.1	12.1	12.1
	Atorvastatin	40	69.0	69.0	81.0
	Simvastatin	1	1.7	1.7	82.8
	Rosuvastatin	10	17.2	17.2	100.0

Table 2
TYPES OF STATINS USED IN THE STUDY

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Without	7	12.1	12.1	12.1
	10 mg	22	37.9	37.9	50.0
	20 mg	18	31.0	31.0	81.0
	40 mg	10	17.2	17.2	98.3
	80 mg	1	1.7	1.7	100.0

Table 3
DOSAGE OF STATINS USED IN THE STUDY

patients were overweight and 25.8% were obese. 53 of the patients included associated type 2 diabetes mellitus insulin dependent.

The mean value for AST was 25.5±17.7 mg/dL, with a maximum of 106 mg/dL, for ALT it was 36.7±36.7 mg/dL, with a maximum of 191.6 mg/dL, for uric acid the mean value was 4.5±1.7 mg/dL, with a maximum of 8.16 mg/dL. As for the lipid profile, mean cholesterol was 145.7±40.4 mg/dL and for tryglicerides was 116.7±56.2 mg/dL (table 1).

Most of the study subjects had statins (87.9%) in the treatment regimen, but there were also patients who did not receive statin therapy at home, even after the cerebrovascular event. Among the statin type, atorvastatin was the most used (69%), then rosuvastatin (17.2%) and simvastatin (1.7%) last (table 2).

Regarding the statin doses used, the most frequent dose was 10 mg (37.9%), followed by 20 mg (31.0%), then 40 mg (17.2%) and only 1.7% of patients were treated with the 80 mg dose (table 3).

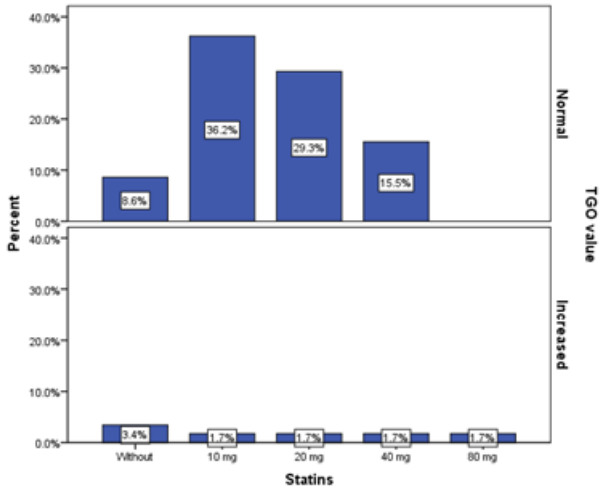

Fig.1 Correlations between dosage of statins and ALT value

Results and discussions

The international guidelines in place for ischemic stroke mention the need for statins to be used as secondary prevention [13]. In our study, 12% of patients did not have chronic statin treatment, 37.9% had statin at the 10 mg dose, 31% had a statin dose of 20 mg, 17.2% had 40 mg of statin and 1.7% had the statin dose of 80 mg. The recommended doses in the European Cardiology Guide are 40 mg, respecting 80 mg in patients with a history of stroke [13]. The same guidelines mention the possibility of decreasing the statin dose when the hepatic enzymes increase by 3-5 times the normal value, 3 weeks after initiation of the statin-lipid lowering regimen. In our study, the altered aspartate aminotransferase (AST) value was found in a similar percentage of 1.7% in patients taking statin of 10 mg, 20 mg, 40 mg or 80 mg. Note that the statistically significant percentage of patients with increased liver enzymes by 3,4% in the absence of hypolipidemic therapy (fig. 1). Among hepatic enzymes, we found a statistically significant correlation between the AST value and the statin dose used ($p = 0.039$).

Another risk factor for vascular disease is the uric acid. In our study, we noticed a statistically significant difference between the uric acid value and the statin concentration used. Thus, elevated uric acid was found in 2% of patients receiving 10 mg statin treatment, the same proportion as patients receiving the 20 mg or 40 mg dose. It should be noted that the uric acid value is not altered when the dyslipidemic treatment is administered at the maximum dose of 80 mg. Increased uric acid was quantified in 6% of patients, decreased in 65.3% of them and normal in 28.7%. The value of uric acid was taken into account in all patients regardless of whether or not they are taking urate-lowering therapy, so it seems that statins, besides their hypolipidemic role, also have a role in lowering the uric acid, a demonstrated cardiovascular risk factor. The statistically significant difference was observed between the statin dose used versus the normal uric acid value ($p = 0.046$) and the elevated uric acid value (fig. 2).

Statin therapy is absolutely mandatory in patients with a history of stroke, especially if they present with diabetes also. Unfortunately, only 8.5% of diabetic patients undergoing insulin treatment were also treated with statin and there was a statistically significant difference between statin dose in diabetic patients, respectively, without diabetes ($p = 0.003$). Patients with oral diabetes mellitus did not show any statistically significant correlation between doses of statins used. Although the percentage

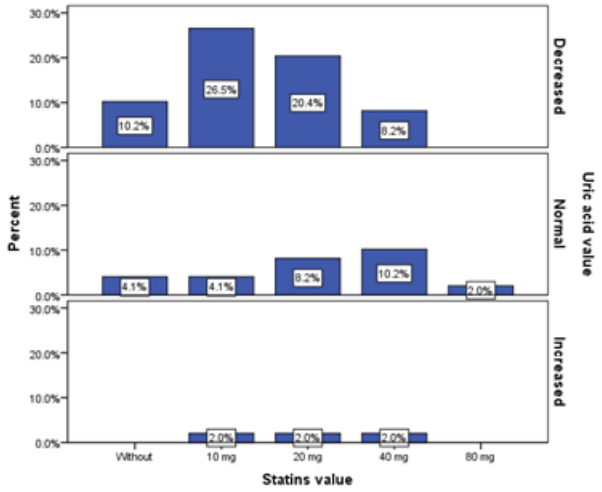

Fig 2. Correlations between statin dose and uric acid value

of diabetic patients receiving dyslipidemic therapy is low, we noticed that most (3.4%) took the 40 mg dose, statistically significant from the other doses used in our patients. The percentage is similar for the 10 mg and 20 mg dose. Note that the 80 mg dose is found only in patients with stroke and diabetes, unfortunately in a low percentage of 1.7% (fig. 3).

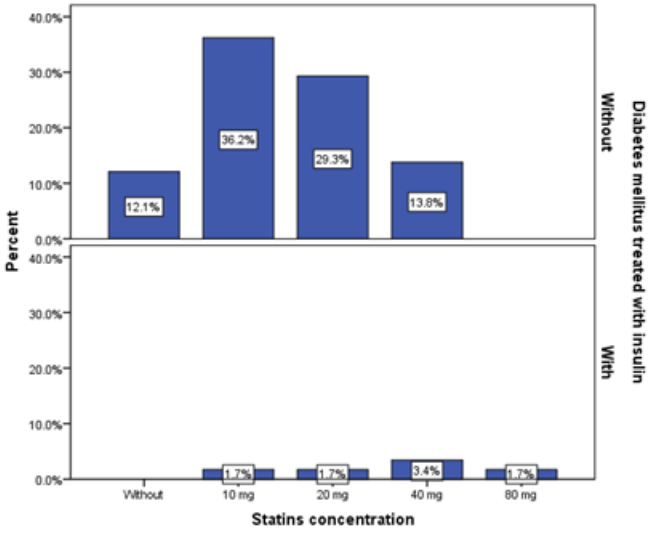

Fig 3. Correlations between statins concentration and presence of diabetes mellitus

According to the recommendations of the international protocols for the secondary prevention management of ischemic stroke patients it is recommended to quantify carotid atheromatosis by cervical Doppler ultrasound. In our study, atheromatosis was found in 53.4% of patients with ischemic stroke. 8.6% did not have statin treatment. There was a statistically significant difference between the percentage of patients with atheromatosis and the percentage of patients without atheromatosis. For the statin dose of 10 mg and 20 mg respectively, the percentage of patients treated with statin but without atheromatosis was statistically significant compared to atherosclerotic patients (22.4% vs 15.5% at the 10 mg dose, respectively 17.2% vs. 13.8% at the 20 mg dose). The percentages are reversed with a statistically significant difference in patients with stroke, atheromatosis and 40 mg statin and patients without atheromatosis. The statin dose of 80 mg, as recommended by the guidelines, was identified in 1.7% of stroke patients with established atheromatosis (fig. 4). So,

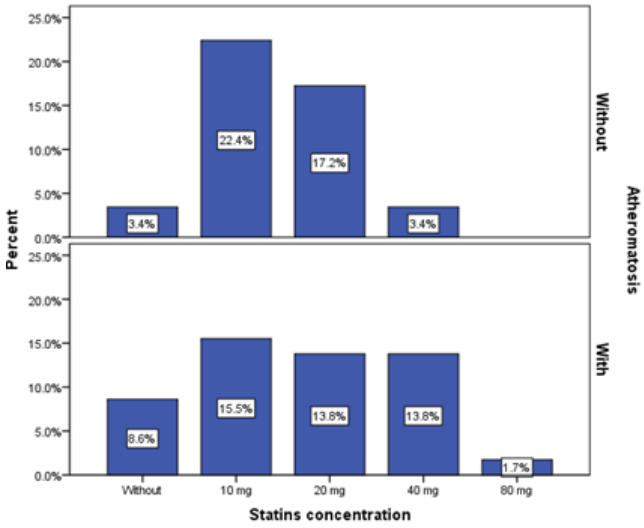

Fig 4. Correlations between statins concentration and atheromatosis

patients with atheromatosis and stroke are treated optimally at a rate of 15.5%. We did not find any statistically significant difference between cholesterol and triglycerides and the statin dose.

Conclusions

In our study, we found a significant link between atheromatosis and statin treatment, more obvious in patients taking a higher dose. We also found a connection between the statin dose and the decrease of uric acid value, another cardiovascular risk factor. So, it is imperative to use statins to lower cholesterol value and to stabilize the atheroma plaque in patients with stroke.

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